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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,678	10/08/2004	Urs Meyer	3024-107	4374

46002 7590 08/24/2007

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
08/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,678	MEYER ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 19-23* is/are pending in the application.

4a) Of the above claim(s) *1-12,19 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-16 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/8/04; 1/10/05, 11/8/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group II (claim 12-16 and 20-22) in the reply filed on 5/23/07 is acknowledged. The traversal is on the ground(s) that 1) as the claimed nucleic acid is claimed in terms of its intended use, this effects the defining technical feature i.e. Example 4 of the PCT international search and preliminary guidelines. This is not found persuasive for the following reasons. Example 4 doesn't consider whether substance X is known in the art. When this fact is considered in a similar fact pattern and the molecule is known, unity does not exist.

"10.21 *Example 1*

Claim 1: A method of manufacturing chemical substance X.

Claim 2: Substance X.

Claim 3: The (method of) use of substance X as an insecticide.

Unity exists between claims 1, 2 and 3. The special technical feature common to all the claims is substance X. However, if substance X is known in the art, unity would be lacking because there would not be a special technical feature common to all the claims."

In the instant case as in example 1, substance X (DR4 site) is known. While applicants argue that the claims include the activity of the nucleic acid is should be considered. As, the claims are drawn to the isolated nucleic acid and one would assume absent evidence to the contrary that the activity of the nucleic acid is an inherent property. As the specification teaches the DR4 sites are required for induction. Hence, a sequence comprising these sequences will mediate the same functions.

2) Applicants argue that the sequences should not be subject to restriction requirement as they share a technical feature or a general inventive concept. A comparison of SEQ ID NO:9 demonstrates that SEQ ID NO:8 encompasses the 5' region of SEQ ID NO:9. As well functionally, the two sequences have some overlapping function relationship as demonstrated in figure 12 and 13. Given the similarity, both claims 8 and 9 will be examined in relation to the instant claims. However, significant structural differences exist between claims 1-7 and 8. In fact, a comparison of SEQ ID NO:8 to SEQ ID NO:s 1-7 and 10 revealed no sequence similarity. A DR-4 sequence and associated function, as demonstrated by the art, is not a novel finding in the art and as such does not constitute a general inventive concept.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-11, 19 and 23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5/23/07.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). Specifically, the address, city and zip of David Frazer as well as the address and sip of Adrian Zumsteg and Michael Podvinec have been altered.

Specification

The disclosure is objected to because of the following informalities: sequences listed in figures 1B, 8, 9, 18A and 18B are not accompanied by SEQ ID NO:s. It would be remedial to add them to the figure or the figure legends.

On page 10, --unknown-- is misspelled as "unknown" in line 28.

Appropriate correction is required.

Claim Objections

Claims 12, 14, 15, 20 and 21 are objected to because of the following informalities: claims 12, 20 and 21 are drawn to non-elected subject matter. The claims should be drafted in independent form.

Claim 12 and 21 recite, "heme and/or p450 cytochromes synthesis". It appears that "cytochromes" should be singular.

Claim 14 recites that enhanced expression is detected by colorimetry etc. For clarity, the claim should be amended to recite that the reporter gene product is detected by colorimetry, fluorescence, radioactivity or chemiluminiscence as it is the protein that is directly detected, which is the product of enhanced expression. Similarly, claim 15 recites that enhanced transcription is detected by quantitative PCR. For clarity, the claim should indicate what is detected by the quantitative PCR i.e. the transcribed nucleic acid encoding the reporter gene.

In claim 16 the word "other" should be deleted for clarity.

Claim 20 recites "at least one testing compound" which should be written as --at least one test compound--. As well in line 5, "adding said at least one testing compound" does not indicate to what the compound is added. Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 12-16 and 20-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12-16 and 20-22 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: in claims 12-16, there are no steps that link that intended use "for testing compounds for modulation of heme and/or p 450 cytochromes synthesis" to the steps. Claim 12 is drawn to methods in which compounds are contacted with a genetic construct comprising a DR-4 nuclear receptor-binding site operably linked to a reporter gene. Repression or enhanced expression and/or transcription are detected. However, it is not clear how the results of repression or expression correlate with the ability of the test compounds to modulate heme and/or p450 cytochrome. Claim 20 suffers from the same inadequacy but additionally lacks other steps. For example claim 20 recites "ascertaining modulation of expression levels in said expression system wherein said modulation is mediated by said nucleic acid sequence". However, the claim sets forth that the expression system is the nucleic acid . As

the claim sets forth that the modulation of the expression system is modulated by itself, it is not clear what expression levels are measured and how the nucleic acid can modulate itself. The dependent claims are included in the rejection because they fail to address or clarify the basis of the rejection as discussed in detail for the independent claims.

Claims 20-22 are vague and indefinite in that the metes and bounds of "an expression system" are unclear. A "expression system" is not defined in the specification. The recitation of "system" implies method steps that are not properly included in a product claim. Therefore, it is unclear if by "system" applicants intend to mean a living organism or a process for obtaining an objective.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-16 and 20-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for testing for enhanced expression of a reporter construct comprising SEQ ID NO:8 or SEQ ID NO:9 operably linked to a reporter gene by a test compound wherein the method is performed *in vivo* (claims 12-16) or the method is performed *in vitro* (claims 20-22), does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

The instant claims are drawn to a nucleic acid sequence comprising at least a DR-4 nuclear receptor binding site wherein said nucleic acid sequence functions as a transcriptional enhancer of the 5-aminolevulinic acid synthase gene for purposes of screening compounds that are capable of activating or repressing transcription from this segment of DNA. The methods are performed *in vivo* or in an "expression system". Neither the claims nor the specification demonstrate a correlation between expression of the molecules comprising at least one DR-4 element (AG(T/G)TC) and heme and/or p450 modulation (enhanced expression or repression). As well, neither the claims nor the specification set forth what relationship between modulation of heme and/or p450 and repression or expression exists. The method uses *any* nucleic acid comprising at least a DR-4 sequences as potential test molecules for the recited methods. The expression system used in claims 20-22 has no explicit components and the undefined nature leaves the claim quite broad. The scope of the invention is extremely broad which is exacerbates the unpredictability of the instant claims.

The MPEP teaches, "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify

the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). The methods are drawn to a method of identifying test compounds for use *in vivo* for the modulation of heme and/or p450 synthesis. The test system comprises in claims 12-16 a cell comprising an isolated nucleic acid operably linked to a reporter gene and in claims 20-22 an expression system comprising just the isolated nucleic acid sequence. The recited nucleic acid constitutes a broad and potentially diverse group of sequences with a minimal requirement of comprising at least one DR-4 nuclear receptor binding site and that function as a transcriptional enhancer of the 5 ALAS gene. Based upon the specification, a DR-4 site is the basic requirement of a sequence to function in this manner. "All experiments done so far, showed that the region containing the DR4 sites was absolutely required to get any induction at all." The specification discloses first large regions of chicken, mouse or human that respond to the prototypical hALASI inducers phenobarbital (PB) and propylisopropylacetamid (PIA) and then from these isolate smaller fragments with similar activity of the larger fragment. In human two distinct large regions are isolated that appear to mediate ALAS mediated induction (SEQ ID NO:9 and SEQ ID NO:10). From SEQ ID NO:9 a smaller 174 base pair region is isolated that has similar properties as the full-length host DNA (SEQ ID NO:8). Several of the fragments are used in a screen for compounds that activate expression from the sequence and compounds capable of activating expression from these fragments were identified. However, methods of identifying compounds that mediate repression are not provided in the specification. While some compounds do not enhance expression these cannot be classified as repressors strictly on their

lack of expression as lack of expression could be due to any number of factors such as compounds that do not bind to the nucleic acids or that bind but do not activate expression. Furthermore, the specification does not contemplate methods of measuring repression.

Considering the broad nature of the claims. The claims are drawn to in claims 12-16, sequences comprising at least a DR-4 nuclear receptor-binding site. The specification teaches, "All experiments done so far, showed that the region containing the DR4 sites was absolutely required to get any induction at all." Hence, any sequence comprising a DR-4 sequence should function as a transcriptional enhancer of ALAS as set forth by the specification. While applicants have argued in response to the lack of unity requirement that a sequence comprising DR-4 is not enough rather what is required of the sequence is that it function as a translational enhancer of ALAS, absent evidence to the contrary, any sequence comprising a DR-4 site should function to act as an enhancer of ALAS. In claims 20-22, the claims are drawn to "an expression system" however, the claims do not set forth the steps or components required of the system.

Even so, it is not clear how the enhanced expression correlates to modulation of heme synthesis and/or P450 synthesis. Applicants only describe an assay system to find modulators of sequences isolated from the 5' region of ALAS such as SEQ ID NO:8. The broad nature of the recited nucleic acids and expression systems used to measure modulation exacerbates the unpredictability that any of the compounds that enhance expression from *any* nucleic acid and *any* expression system comprising a DR-4 site will also modulate hem synthesis and/or p450 synthesis.

The invention recites use of a broad group of nucleic acids, expression systems and cells to measure modulation of heme and/or p450. Given the unpredictability of the art, the poorly

developed state of the art with regard to predicting the structural/ functional characteristics of antagonists, the lack of adequate working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 12-14, 16, 20 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Liao and Song (US 5,639,616; see entire document).

Liao and Song teach a construct comprising a DR-4 as evidenced by Chang and Pan (see page 196, col 2, ¶ 3). The construct was used to measure expression of a reporter gene in the presence of test compounds such as RXR, UR and retinoic acid. Such compounds can be considered to be candidate drugs. Expression was measured by measuring radioactivity (see e.g. figure 5b).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Maria B Marvich, PhD
Examiner
Art Unit 1633